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Primer

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Prediabetes

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Abstract

Prediabetes or intermediate hyperglycaemia represents a preliminary stage in the development of type 2 diabetes mellitus (T2DM). In addition to an increased likelihood of developing T2DM, individuals with prediabetes have an elevated risk of various vascular and non-vascular complications. No consensus has been achieved on the ideal screening strategy for prediabetes, with fasting plasma glucose concentration, glycated haemoglobin (HbA1c) and the oral glucose tolerance test being the most frequently measured parameters. The two major phenotypes of prediabetes, that is, impaired fasting glucose and impaired glucose tolerance, may represent different pathophysiologies with varying natural history, risk of adverse outcomes and responsiveness to treatment. Most of the evidence for managing prediabetes focuses on lifestyle modification with or without medications in individuals with overweight or obesity and impaired glucose tolerance. Whether these interventions are beneficial in individuals with impaired fasting glucose and those of normal body weight is unclear, as is the cost-effectiveness and sustainability of pharmacotherapy for treating prediabetes. Large-scale national T2DM prevention programmes are currently under way to assess whether the benefits of interventions for prediabetes can be translated to the community setting.

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Introduction

Diabetes mellitus is a metabolic and vascular disorder characterized by chronic hyperglycaemia associated with cellular and vascular damage, resulting in various complications and associated with considerable morbidity and premature mortality. In type 2 diabetes mellitus (T2DM), the most common form of diabetes mellitus, progressive increases in blood glucose levels are often detected before the cutoffs for diagnosing diabetes mellitus are reached. Thus, the terms 'prediabetes' or 'intermediate hyperglycaemia' have been introduced to classify individuals with blood glucose levels above those used to define normoglycaemia but below the current thresholds for diagnosing diabetes mellitus (Table 1). Multiple definitions of the categories of intermediate hyperglycaemia exist (Box 1). Although the WHO and the International Diabetes Federation have used the term intermediate hyperglycaemia as a collective term for all these categories, the term 'prediabetes' is used in this Primer as it is more familiar to clinicians and communities. Individuals with prediabetes are at higher risk of developing T2DM as well as vascular and other complications than those with normal blood glucose levels[1].

People with prediabetes and early stages of diabetes often do not have symptoms and their diagnoses are entirely based on predefined values of fasting plasma glucose, 2-h plasma glucose during the oral glucose tolerance test (OGTT) and/or glycated haemoglobin (HbA1c)[2]. Prediabetes can be detected using a measure of one or more of the following – a fasting plasma glucose value (after an overnight fast of at least 8 h), plasma glucose values after 2 h during a 75-g oral glucose load (that is, the OGTT) or HbA1c. The latter can be simply explained as the proportion of the β-chains of haemoglobin to which glucose has been non-enzymatically added ('glycated')[3]. Since the red blood cells have a turnover period of 2–3 months, HbA1c provides an estimate of the mean blood glucose levels that the red blood cells have been exposed to during the same period.

Impaired fasting glucose (IFG) is characterized by fasting plasma glucose values that are above normal levels but not sufficiently elevated to be diagnostic of diabetes mellitus. Similarly, impaired glucose tolerance (IGT) refers to individuals with 2-h plasma glucose levels (during an OGTT) that are above normal but not so high as to warrant a diagnosis of diabetes mellitus. Individuals may have IGT or IFG in isolation or may present with combined IGT and IFG. The measure of HbA1c has an advantage over plasma glucose levels as it reflects long-term glycaemic control and is not subject to day-to-day variation; however, due to limitations and pitfalls (for example, in patients with anaemia or during pregnancy), HbA1c is not universally accepted for diagnosis of prediabetes. The diagnostic criteria for prediabetes are based on epidemiological, mechanistic and intervention studies linking these thresholds to the risk of progression to T2DM and cardiovascular disease (CVD) (Box 1).

Given the hundreds of millions of people with high blood glucose encountered by many health-care providers, knowledge of prediabetes is of great importance to the practising physician, as correct diagnosis offers a golden opportunity for monitoring, education and early intervention, which can favourably alter its trajectory. In this Primer, we provide a broad overview of prediabetes, discussing its epidemiology, our current understanding of its pathophysiology, diagnosis, implications, and management and propose avenues for further research to improve patient outcomes.

Table 1 | Definitions of prediabetes

Organization	IFG based on fasting plasma glucose	IGT based on 2-h glucose value during an OGTT	At risk of diabetes based on HbA1c	Ref.
ADA	5.6–6.9 mmol/l (100–125 mg/dl)	7.8–11.0 mmol/l (140–199 mg/dl)	5.7–6.4% (39–46 mmol/mol)	2
WHO	6.1–6.9 mmol/l (110–125 mg/dl)	7.8–11.0 mmol/l (140–199 mg/dl)	NA	208
IEC	NA	NA	6.0–6.4% (42–46 mmol/mol)	209

ADA, American Diabetes Association; HbA1c, glycated haemoglobin; IEC, International Expert Committee; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NA, not applicable; OGTT, oral glucose tolerance test.

Epidemiology

Prevalence and incidence

In 2024, the International Diabetes Federation estimated that, globally, in addition to 589 million adults with diabetes mellitus (the majority having T2DM), 634.8 million adults (12.0% of adults worldwide) have IGT and 487.7 million adults (9.2% of the global adult population) have IFG[4]. One review[5] revealed that the global prevalence of IGT was almost twice that of IFG (9.1% versus 5.8%, based on the WHO definition of IFG). The highest prevalence of IGT was found in the North American and Caribbean regions and that of IFG in the South-East Asia region. The prevalence of IGT was higher than that of IFG worldwide, except in the South-East Asia region[5] (Fig. 1).

However, the different definitions used for prediabetes lead to considerable variations in estimates of its prevalence and incidence. Different groups of people are identified by different definitions of prediabetes because of the limited overlap and the influence of age, sex and ethnicity on the results of diagnostic tests, as identified in a 2006 review[6]. The prevalence of both IGT and IFG increases with age. IFG is typically more common in men than in women, whereas IGT is more common in women than in men. The observed sex differences in prevalence are most marked in people <55 years of age[6]. The overlap between the two forms of prediabetes (that is, those with IFG and IGT) is limited. Studies cited in the 2006 review identified that the proportion of people with IGT who also have IFG varied from 13.4% in a Korean population to 26–27% in European and USA populations. The proportion of individuals with IFG who have IGT varied from ~31% in European and Australian populations to 50–60% in Pima Indian, Chinese and Korean populations. Similar discordance is likely to be observed between fasting glucose and HbA1c-defined categories for prediabetes (as has been identified for diabetes). In most low-income and middle-income regions, isolated elevated HbA1c was found to be more common than isolated elevated fasting plasma glucose[7]. Global estimates of the prevalence of prediabetes using HbA1c do not exist, partly owing to the limited use of HbA1c in many countries as a consequence of its cost, and limited value in populations with high prevalence of anaemia in addition to limited availability of data from population-based studies that also affect glucose-based estimates of prediabetes. In a population-based study of the 70% of long-term residents of Denmark of 20–100 years of age who had at least one HbA1c measurement, the overall prevalence of prediabetes defined by HbA1c of 42–47 mmol/mol (6.0–6.4%) was 7.1% (95% CI 7.1–7.1%)[8]. Data from the National Health And Nutrition Examination Survey (NHANES) in the USA show that age-standardized prevalence of prediabetes (defined by HbA1c of 5.7–6.4% or fasting plasma glucose level of 100–125 mg/dl) increased from 29.5% to

48.3% between 1999 and 2018 (ref. 9), indicating a steady rise in the prevalence of prediabetes.

Progression to T2DM

The various forms of prediabetes differ in their risk of progressing to T2DM. Individuals who have combined IFG and IGT have the highest incidence of T2DM, followed by those who have isolated IGT and then those with isolated IFG with no clear geographic differences[10]. The rate of progression from prediabetes to T2DM is further influenced by additional risk factors that can interact to accelerate progression, calling for comprehensive and individualized risk assessment in people with prediabetes[10].

Risk factors

Risk factors for prediabetes are the same as those for T2DM[5,11–15]. The non-modifiable ones include increasing age, sex (IFG is more common in men than women, IGT is more common in women and HbA1c is generally higher in women than in men), ethnicity or race (lower risks are observed in white individuals than in other populations), family history, extremes of birthweight and genetic factors. Modifiable risk factors, many of which are associated with urban living, economic development and socio-economic status, include physical inactivity, unhealthy diet (for example, sugar-sweetened beverages, highly processed foods and high consumption of red meat), smoking and excessive alcohol intake[11–15]. Other psychological and behavioural factors include poor sleep, stress, anxiety, depression and poor quality of life. Obesity (particularly central obesity as reflected by higher waist circumference) is a key mediator of the effects of some of the most important risk factors and is also associated with high blood pressure and abnormal lipid levels. Evidence suggests that sex differences exist in the relative association of risk factors for prediabetes, with central obesity, abnormal lipid levels, smoking and alcohol consumption being key risk factors in men and high blood pressure and low-quality diets being relatively more important for women. Additional risk factors for women include history of gestational diabetes and polycystic ovary syndrome[15].

Morbidity and mortality

An umbrella review of 16 systematic reviews[16] showed that IGT-defined prediabetes and IFG-defined prediabetes but not HbA1c-defined prediabetes were associated with an increased risk of all-cause mortality compared with normoglycaemia defined by the same measure. The postulated reasons for this discrepancy include the low number of studies with HbA1c-defined prediabetes as well as the likelihood of elevated HbA1c being a less robust measure of high blood glucose in individuals with normoglycaemia and prediabetes in comparison to those with diabetes. Risk of all-cause mortality, coronary heart disease and stroke was higher for IGT than for IFG[16]. The frequent coexistence of prediabetes with multiple risk factors (for example, obesity, high blood pressure, abnormal lipids, insulin resistance (a condition of suboptimal response to insulin actions), low estimated glomerular filtration rate, albuminuria, metabolic dysfunction-associated steatotic liver disease (MASLD), ischaemic heart disease and heart failure) contribute to the high risk for multiple morbidities and premature death in people with prediabetes[17].

Mechanisms/pathophysiology

Physiology of insulin sensitivity and secretion

Under physiological conditions, blood glucose is maintained within a narrow range (normoglycaemia) mainly by timely insulin secretion and action as well as the availability of metabolites such as glucose, branched-chain amino acids and non-esterified fatty acids (NEFA) (Fig. 2). In the absence of nutrient intake (as occurs in the fasting state), blood glucose levels are prevented from dropping too low by a decrease in insulin secretion, which reduces glucose uptake in skeletal muscle and adipose tissue[18]. This reduced uptake along with elevated glucagon levels, initially favours hepatic glycogenolysis (that is, the breakdown of glycogen to glucose) and subsequently gluconeogenesis (which is the synthesis of glucose from non-carbohydrate substrates). Current studies point to a specific role of increased adipose tissue lipolysis due to hypoinsulinaemia and increased glucocorticoid secretion, giving rise to circulating NEFA, which allosterically stimulate gluconeogenesis, and glycerol, which serves as a gluconeogenic substrate in the liver[18]. Upon carbohydrate ingestion, the increase in blood glucose induces insulin

Box 1 | Evolution of the definition of prediabetes

Impaired glucose tolerance (IGT) was first defined in 1979–1980 by the National Diabetes Data Group in individuals who had a plasma glucose level ≥7.8–11.1 mmol/l (140–199 mg/dl) at 2 h during a 75-g oral glucose tolerance test but a fasting plasma glucose level below the threshold diagnostic of diabetes mellitus (<7.8 mmol/l (<140 mg/dl)); the fasting plasma glucose level cut-off was subsequently revised to <7.0 mmol/l (<126 mg/dl))[212,213]. The definition of IGT was supported by the association of increased 2-h plasma glucose level during the oral glucose tolerance test, that is, 2-h plasma glucose ≥7.8 mmol/l (≥140 mg/dl), with incident microvascular complications[214]. Similar findings have also been reported in a prospective survey based on the UK Whitehall study[215].

In 1997, an international expert committee introduced the term impaired fasting glucose (IFG), defined as a fasting plasma glucose level of 6.1–6.9 mmol/l (110–125 mg/dl), which was associated with increased risk of incident cardiovascular disease[209]. In 2003, the American Diabetes Association lowered the fasting plasma glucose level cut-off for IFG from 6.1 mmol/l (110 mg/dl) to 5.7 mmol/l (100 mg/dl)[216]. However, the WHO and the International Diabetes Federation continue to recommend a fasting plasma glucose level range of 6.1–6.9 mmol/l to define IFG[217].

Glycated haemoglobin (HbA1c) has been widely used to monitor diabetes control since the 1980s. However, improvement in standardization of the HbA1c assay (such as those promoted by the National Glycohemoglobin Standardization Program) led to a widening of the scope of use of this test, culminating in a 2009 report on the role of HbA1c to diagnose diabetes mellitus[208]. The international expert committee also recommended that individuals with HbA1c levels above the upper limit of normal but below the diagnostic threshold for diabetes mellitus should be considered as being at high risk of developing diabetes mellitus and receive effective interventions to delay or prevent the onset of diabetes. They defined this 'high risk' group by an HbA1c range of 6.0–6.4% (42–47 mmol/mol). In 2010, the American Diabetes Association lowered the range to 5.7–6.4% (39–47 mmol/mol) to better identify individuals with IGT and IFG and those at high risk of cardiovascular disease[218]. However, the use of HbA1c to identify prediabetes has not been endorsed by the WHO[208].

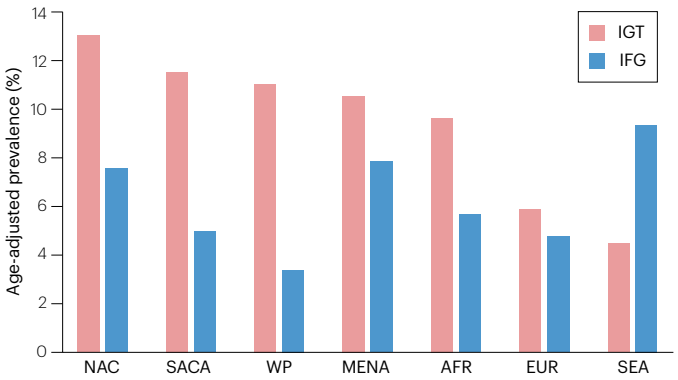

Fig. 1 | Global prevalence of prediabetes. Global age-adjusted prevalence of prediabetes in 2021 split by region and category (impaired glucose tolerance (IGT) or impaired fasting glucose (IFG)). Data were originally presented in ref. 5. AFR, Africa; EUR, Europe; MENA, Middle East and North Africa; NAC, North American and Caribbean; SACA, South and Central America; SEA, South-East Asia; WP, Western Pacific.

secretion from pancreatic β-cells, following a two-phase pattern. The first phase, occurring in the first 10 min after carbohydrate ingestion, represents the release of pre-stored insulin from islet vesicles whereas the second phase, occurring during the subsequent 2–3 h, is characterized by the release of newly synthesized insulin and replenishment of islet cell insulin stores[19]. High levels of insulin mainly stimulate skeletal muscle glucose uptake and storage as glycogen but also favour NEFA uptake and esterification to triglycerides in adipose tissue. Hyperinsulinaemia, along with suppression of glucagon, by insulin and incretins, such as glucagon-like peptide 1 (GLP1) and glucose-dependent insulinotropic polypeptide (GIP)[20–22], favour hepatic glycogen storage and decrease gluconeogenesis, collectively reducing endogenous glucose production and maintaining normoglycaemia. At a cellular level, insulin action allows for the uptake of glucose, amino acids, and NEFA and the synthesis of storage forms of these metabolites such as glycogen, proteins and triglycerides, respectively. During meal ingestion or an OGTT, skeletal muscle accounts for the vast majority of glucose uptake and non-oxidative storage as glycogen[18]. The interaction of insulin with its receptor initiates a cascade of phosphorylation events, ultimately activating AKT (protein kinase B), which collectively favours the recruitment of intracellular vesicles containing glucose transporters (GLUT4) to the cell membrane, thereby stimulating glucose uptake (Fig. 2). In parallel, activated AKT2 inhibits glycogen synthase kinase (GSK3α/β), leading to disinhibition of glycogen synthase and stimulation of glycogen synthesis from glucose-6-phosphate[18,23–26].

Aetiology of prediabetes

The almost 100% concordance rate of lifetime risk of T2DM in monozygotic twins underlines the importance of inherited factors[27]. In line with this finding, genome-wide association studies revealed many genetic loci that are linked to the biology of pancreatic islets, skeletal muscle and adipose tissue[28,29]. Other studies have reported associations of genetic risk scores, implicating the role of β-cell pathways in prediabetes development[30,31]. However, these genetic variants explain <20% of T2DM risk[30,31], suggesting that demographic factors, for example, age, sex, ethnicity, ancestry, and transgenerational and early perinatal epigenetic modifications (for example, intrauterine environment and extremes of birthweight) can contribute to the predisposition to developing prediabetes[32–34]. Furthermore, lifestyle factors, environmental conditions and life-course events may precipitate the progression from normoglycaemia to prediabetes and T2DM, which can be modified by early diagnosis and intervention[35]. In addition, intestinal dysbiosis (that is, the abnormal composition of gut microbiota) alters the release of short-chain free fatty acids, proteins, vitamins and secondary bile acids into the circulation, which can contribute to insulin resistance, prediabetes and T2DM[36]. Weight loss studies in humans provided evidence that reduction of insulin resistance and visceral adipose tissue mass are the primary drivers of the remission of prediabetes and T2DM[37], consequently underlining the predominant role of insulin resistance and adipose tissue dysfunction in the onset and progression of prediabetes.

The model of integrative biology of the development of T2DM postulates that the initial events of insulin resistance comprise local mechanical stress and hypoxia leading to infiltration of macrophages in adipose tissue contributing to its dysfunction[18]. Dysfunctional adipose tissue is characterized by local inflammation and insulin resistance with impaired insulin-stimulated lipogenesis, favouring the secretion of NEFA and pro-inflammatory adipokines over the secretion of anti-inflammatory (insulin-sensitizing) adipokines[18]. In the Whitehall II study, the reduction of circulating levels of adiponectin, an insulin-sensitizing adipokine from mature subcutaneous adipose tissue, observed decades before T2DM onset, supports the role of adipose tissue dysfunction in prediabetes[38]. Over time, these alterations lead to systemic insulin resistance, low-grade (subclinical) inflammation and ectopic lipid accumulation, characterized by visceral adiposity and MASLD[18]. Prediabetes and MASLD share further similarities such as intestinal dysbiosis[39] and impaired mitochondrial adaptation[40]. Of note, the mutual relationship between MASLD and prediabetes is illustrated by longitudinal analyses, showing a hazard ratio of 1.69 for prediabetes in individuals with MASLD[41].

Dysglycaemia and progression to T2DM

In prediabetes, a gradual rise in glycaemia occurs despite increased insulin secretion in the face of insulin resistance. In this regard, individuals with prediabetes frequently exhibit insufficient first-phase insulin secretion with increased late-phase insulin secretion to overcome the earlier hyperglycaemia. This excessive burden on β-cell function eventually leads to its decompensation with overt hyperglycaemia[42,43]. Studies using OGTTs along with assessment of insulin sensitivity and β-cell function revealed the heterogeneity of the trajectories of dysglycaemia (abnormal blood glucose levels)[44]. The UK Whitehall II study monitored the changes in insulin sensitivity and plasma glucose levels in civil servants of mainly European ancestry for almost two decades at the end of the twentieth century (a time period indicating the start of marked increases in obesity prevalence in the UK)[44]. Although individuals who did not develop diabetes mellitus only showed a gradual decline in whole-body insulin sensitivity with stable β-cell function, those developing T2DM exhibited markedly reduced insulin sensitivity more than 10 years before diabetes onset (Fig. 3). This reduced sensitivity was accompanied by a continuous rise in the fasting plasma glucose and post-OGTT plasma glucose levels albeit within the normoglycaemic range. At ~6 years prior to the onset of T2DM, a steep increase in the post-challenge glycaemia occurred, which was followed (at around 2 years prior to the onset of T2DM) with a similar steep rise in fasting glycaemia[44]. Several other cohorts have reported similar phenomena[45–47] with variations amongst ethnic groups exhibiting different time course patterns of these changes[48]. These changes are

paralleled by a multistage model of β-cell dysfunction occurring on the background of insulin resistance[49] (Fig. 3). This finding also highlights the importance of identifying early abnormalities in insulin action and secretion before the onset of dynamic changes leading to persistent hyperglycaemia.

Insulin resistance and β-cell dysfunction

Models of prediabetes. Reflecting the relative roles of insulin resistance and β-cell dysfunction, different models have been used to explain the β-cell dysfunction in prediabetes and T2DM (Fig. 4). The most widely accepted model postulates that there is compensatory (secondary) hyperinsulinaemia in response to obesity and obesity-associated insulin resistance, which in the presence of unfavourable genetic variants in genes implicated in β-cell biology and insulin secretion would lead to prediabetes and T2DM (Fig. 4). An alternative school of thought suggests that the primary defect is hyperinsulinaemia owing to overstimulation by environmental and genetic factors, with the subsequent development of obesity and insulin resistance and, subsequently, T2DM upon β-cell exhaustion[50] (Fig. 4). Finally, primary β-cell dysfunction leading to (relative) hypoinsulinaemia could give rise to elevated levels of circulating glucose and NEFA with or without inducing insulin resistance[50,51]. This model may help to explain the insulin-deficient clusters of prediabetes and diabetes[52–54] (Fig. 4).

The role of tissue-specific insulin resistance differs between the fasting state and postprandial state and thereby between IFG and IGT (Fig. 5). In isolated IFG, the increase in fasting glucose concentrations is due to increased endogenous (hepatic) glucose production, which is caused by hepatic insulin resistance and excessive NEFA flux from adipose tissue (Fig. 5). Hepatic insulin resistance comprises impairment of suppression of gluconeogenesis and impairment of stimulation of glycogen synthesis. Elevated cellular NEFA availability allosterically activates gluconeogenic flux, whereas glycerol acts as a substrate of de novo synthesis of glucose from carbon-3 compounds, further increasing gluconeogenesis and glucose production[18]. In the liver as well as in other insulin-responsive tissues, NEFAs stimulate β-oxidation, increase oxidative stress, promote ectopic triglyceride storage, activate ceramide-induced inflammatory pathways[24,25] and inhibit insulin signalling via the PKC–DAG pathway[18,23–26], which further contributes to hepatic insulin resistance. Of note, race-dependent differences in the prevalence of IFG, being lowest in African-Americans, underline the role of ectopic lipid storage[55]. African-American individuals exhibit lower ectopic lipid content in abdominal visceral adipose tissue and liver and lower serum triglycerides than Hispanic or white individuals[56]. Despite the similar degree of overall insulin resistance, African-American women also exhibit lower rates of gluconeogenesis than white women, altogether explaining their decreased fasting glycaemia[57]. In isolated IGT, the increase in postprandial or post-OGTT glucose concentrations is due to impaired peripheral (mainly skeletal muscle) glucose disposal (Fig. 5). This skeletal muscle insulin resistance is characterized by decreased insulin-stimulated glucose transport, phosphorylation and glycogen storage. Aside from rare mutations in the insulin signalling cascade, cellular insulin resistance mainly results from NEFA-derived lipid metabolites such as specific diacylglycerols and ceramides causing lipotoxicity. However, certain amino acids (mainly branched-chain amino acids) and even glucose per se (glucotoxicity) can also inhibit insulin signalling[18,23–26]. Of note, increased intestinal glucose absorption[42] and impaired incretin secretion with decreased prandial insulin release[58] contribute to postprandial glucose excursions.

During progression of prediabetes, other mechanisms of chronic insulin resistance include glucotoxicity, abnormal mitochondrial function[23] and disrupted inter-tissue communication[23–26], culminating in subclinical systemic inflammation[26] with increased release of highly sensitive CRP and other pro-inflammatory cytokines (for example, IL-6 and TNF), which can inhibit the insulin signalling cascade and interfere with proximal insulin signal transduction, leading to insulin resistance.

Of note, impaired insulin secretion or impaired secretory response to metabolic and endocrine stimuli, that is, β-cell dysfunction, can result from primary intra-islet abnormalities such as altered insulin release per se, dysregulated processing of pro-insulin, pro-islet amyloid polypeptide and proglucagon[59], impaired suppression of glucagon by insulin and incretins[60], and variable incretin secretion patterns[61]. Interestingly, despite the well-known glucose-lowering effects of GLP1 and GIP receptor agonists, the circulating levels of these gut peptides are not uniformly altered in prediabetes and T2DM, despite one study reporting lower glucose-challenge responses of plasma GLP1 levels in individuals with combined IGT and IFG than in those with normal glucose tolerance, isolated IFG or isolated IGT[61].

Specific subtypes and novel clusters of prediabetes. The postulated models of β-cell dysfunction and insulin resistance also form the basis of the different prediabetes subtypes. As noted above, IFG is associated with greater hepatic insulin resistance than IGT with reduced early-phase insulin secretion following a glucose challenge[49,62] (Fig. 5). On the other hand, IGT is mainly associated with skeletal muscle insulin resistance with only modest changes in hepatic insulin sensitivity[6] along with impairment of both early-phase and late-phase insulin secretion[62–64] (Fig. 5). Conversely, persons with impaired HbA1c show higher insulin sensitivity and insulin secretion rates than those with prediabetes defined according to glucose criteria[63,64]. The Innovative Medicines Initiative-DIabetes REsearCh on patient straTification (IMI DIRECT) Consortium demonstrated higher rates of progression to T2DM in those with double defects (any two out of IFG, IGT or abnormal HbA1c) than those with isolated defects (OR 3.03) and in those with all three defects than in those with double defects (OR 2.18)[64]. No significant differences in progression to T2DM were observed between groups with a similar number of defects. Moreover, sex dimorphism, such as the higher prevalence of IFG in men and that of IGT in women, along with genetic variability, may further explain the heterogeneity in metabolic and glycaemic changes among individuals with prediabetes[65].

Current studies have introduced novel concepts of deconvoluting and refining prediabetes. In a Central European cohort study, people with increased diabetes risk, of whom 50% had prediabetes, could be allocated to six clusters based on genetic risk scores, glycaemia, low-density lipoprotein cholesterol, hepatic lipid content, adipose tissue compartments, insulin resistance and secretion[52]. Among the six clusters identified, clusters 3 and 5 were shown to have imminent T2DM and increased CVD risk[66]. Of these, cluster 3 showed a high genetic risk score and hypoinsulinaemia, suggesting the need for early β-cell protection and later insulin treatment. Cluster 5 featured insulin resistance and ectopic lipid accumulation, suggesting the need for intensified lifestyle modification and weight loss. Cluster 6, which showed moderate T2DM risk, was characterized by hyperinsulinaemia, ectopic fat accumulation and excessive risk of chronic kidney disease (CKD) and all-cause mortality, suggesting the need for intensified risk factor control. Similar results were reported in the KORA F4/F44 cohort, comprising individuals without T2DM aged 61–82 years[67]. Interestingly,

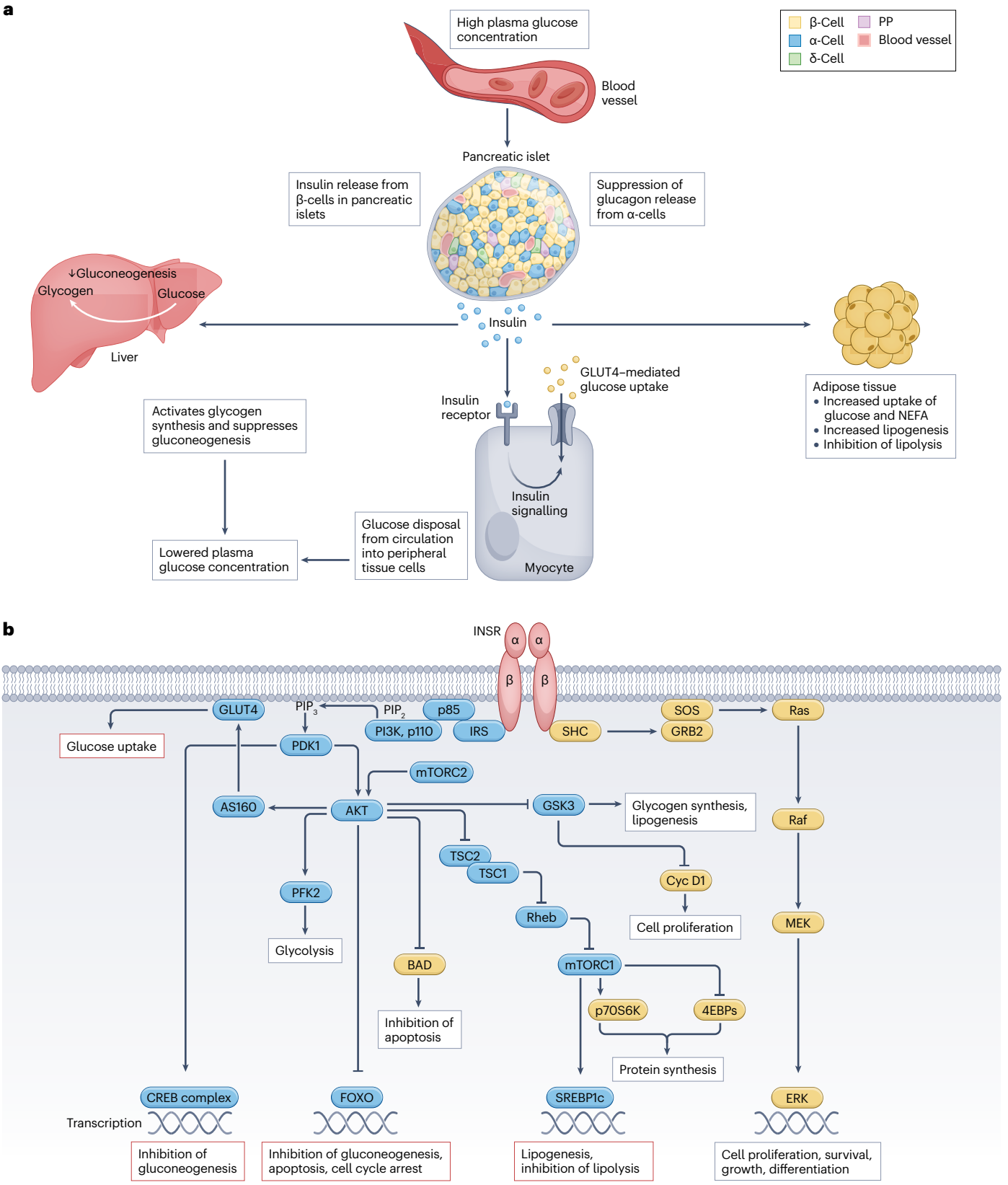
a
High plasma glucose concentration
Blood vessel
β-Cell
α-Cell
δ-Cell
PP
Blood vessel
Pancreatic islet
Insulin release from β-cells in pancreatic islets
Suppression of glucagon release from α-cells
↓Gluconeogenesis
Glycogen
Glucose
Liver
Insulin
GLUT4–mediated glucose uptake
Insulin receptor
Adipose tissue
• Increased uptake of glucose and NEFA
• Increased lipogenesis
• Inhibition of lipolysis
Activates glycogen synthesis and suppresses gluconeogenesis
Insulin signalling
Glucose disposal from circulation into peripheral tissue cells
Lowered plasma glucose concentration
Myocyte
b
INSR
α
α
β
β
GLUT4
Glucose uptake
PIP3
PIP2
p85
PI3K, p110
IRS
SHC
SOS
GRB2
Ras
PDK1
mTORC2
AS160
AKT
GSK3
Glycogen synthesis, lipogenesis
Raf
TSC2
TSC1
Cyc D1
PFK2
Rheb
Cell proliferation
MEK
Glycolysis
BAD
mTORC1
Inhibition of apoptosis
p70S6K
4EBPs
Protein synthesis
CREB complex
Transcription
FOXO
SREBP1c
ERK
Inhibition of gluconeogenesis
Inhibition of gluconeogenesis, apoptosis, cell cycle arrest
Lipogenesis, inhibition of lipolysis
Cell proliferation, survival, growth, differentiation

Fig. 2 | Regulation of glycaemia and insulin signalling. a, Maintenance of normal glucose levels involves a complex interplay of hormonal changes resulting in a balance between glucose entry into the circulation and its disposal into the cells. Elevated plasma glucose levels lead to insulin release from pancreatic β-cells and suppression of glucagon secretion from α-cells. Insulin stimulates entry of glucose into target tissues (especially skeletal muscle) by increased synthesis and availability of glucose transporter 4 (GLUT4). Insulin also inhibits endogenous glucose production from the liver by suppressing gluconeogenesis and stimulating glycogen synthesis, which return plasma glucose levels to baseline. **b**, Binding of insulin to its receptor phosphorylates insulin receptor substrate (IRS), which in turn activates PI3K, which then phosphorylates PIP_2 to PIP_3. PIP_3 then activates AKT3, which, through numerous downstream events, promotes the metabolic actions of insulin as well as some of the mitogenic effects. However, the mitogenic effects are mainly mediated through a different second messenger system, involving binding of the SH2 domain-containing adaptor (SHC) to the insulin receptor (INSR) and activation of the Ras–MAPK–ERK signalling pathway. Insulin resistance chiefly involves the PI3K-mediated pathways. NEFA, non-esterified fatty acids; PP, pancreatic polypeptide. Part **b** reprinted from ref. 211, Springer Nature Limited.

prospective analyses over 6.5–8.3 years showed cluster-dependent differences in CKD and diabetic neuropathy but not in CVD or all-cause mortality[67]. Another independent clustering approach also identified six prediabetes clusters in a large Chinese study[68]. These reports highlight the complexity underlying progression from prediabetes to T2DM similar to the subtypes of T2DM[53], which have been validated and refined in other ethnic groups[69–73].

Comorbidities and complications

An umbrella review of 95 meta-analyses of prospective studies compared summary hazard ratios of outcomes in otherwise healthy persons with prediabetes and individuals with normoglycaemia[16]. Prediabetes (defined by IFG and/or IGT) was associated with an increased risk of all-cause and cardiovascular mortality (summary HR 1.08–1.25 and 1.20–1.30) as well as vascular or myocardial complications (for example, cardiac events, stroke, heart failure and atrial fibrillation). An increased risk was also found for several cancers, mainly hepatocellular cancer and pancreatic cancer (1.23–2.01 and 1.22–1.25, respectively), and dementia from different causes, including Alzheimer and vascular dementia (1.18–1.47). Evidence also showed increased risk for CKD (0.97–1.25)[16], but the evidence for increased risk of peripheral[74] and cardiac autonomic neuropathy[75] and retinopathy[76] was less robust, probably due to the lower number of studies describing these complications. Finally, MASLD is involved in the pathogenesis of prediabetes and metabolic syndrome as reflected by the new nomenclature[77]. Dysglycaemia contributes to the relationship between liver lipid content and insulin resistance with hepatic oxidative metabolism[78]. In turn, prediabetes confers an increased risk for higher grades of portal inflammation and fibrosis (adjusted odds ratios 1.8 versus 2.4)[79].

As to drivers of prediabetes-related complications, the Whitehall II cohort revealed distinct trajectories of cardiometabolic risk factors before diabetes onset[80]. In individuals with IGT, reducing blood glucose levels early had long-lasting effects in reducing progression to T2DM and major events, including all-cause death and vascular complications. Apart from the role of the gradual rise in glycaemia, low-grade inflammation, insulin resistance, oxidative stress and abnormal cellular bioenergetics contribute to the pathogenesis of prediabetes-related complications, including CKD[81], peripheral and autonomic neuropathy[82–84] and, to a lesser extent, retinopathy[85].

Diagnosis and screening

Assessing glycaemia

Hyperglycaemia can be assessed using fasting plasma glucose, 2-h OGTT plasma glucose level or HbA1c (Box 1 and Table 1).

HbA1c. The use of a single non-fasting blood sample has made HbA1c a popular test for diagnosing T2DM and prediabetes in non-resource-constrained settings. However, the different cut-off values of HbA1c, fasting plasma glucose and 2-h OGTT plasma glucose levels have different discriminatory and prognostic values that vary between populations[2]. Use of non-standardized assays of HbA1c as well as qualitative and quantitative variations in blood haemoglobin also contribute to the poor correlation between HbA1c and prevailing blood glucose levels in some populations[86]. Conditions that modify red cell turnover, such as haemolytic anaemia, CKD, splenectomy and certain drugs, can alter the relationship between blood glucose and HbA1c and render the test inaccurate. For instance, HbA1c cannot be used at all for the diagnosis and monitoring of glycaemia in conditions such as sickle cell disease and compound heterozygote states of haemoglobin variants such as HbSC, whereas heterozygous states, such as sickle cell trait, may cause method-dependent interference with the HbA1c assay[87]. Another condition that can interfere with HbA1c measurements is glucose-6-phosphate dehydrogenase (G6PD) deficiency[88], involving an enzyme that helps prevent oxidative stress-induced haemolysis. The above conditions are relatively frequent in discrete geographical locations such as Africa, South Asia, the Middle East and the Mediterranean region, and should be considered when evaluating individuals originating from these locations. Even in the absence of these interfering conditions, the effects of prevailing plasma glucose level on the processes of protein glycation may differ by ethnicity within the normal plasma glucose range due to as-yet uncertain mechanisms[89]. In native and American Africans, the use of HbA1c could miss as many as 50% of people with prediabetes or diabetes. Although this could, in part, be owing to the high prevalence of haemoglobinopathies and sickle cell anaemia[90,91], evidence suggests that these discrepancies persist even in the absence of such confounders. These differences, albeit small, affect the accuracy of HbA1c as a diagnostic test for T2DM or prediabetes and their prognostic significance.

Diabetes and prediabetes aside, the prognostic significance of HbA1c, fasting glucose and 2-h plasma glucose on cardiovascular events and all-cause death also vary amongst populations and settings. Overall, plasma glucose seemed to be more robust than HbA1c in predicting all-cause death in people without diabetes. However, high HbA1c predicted CVD often due to the co-occurrence of other cardiometabolic risk factors[92]. Several reports indicate that fluctuation in fasting plasma glucose predicted mortality[93] whereas 2-h plasma glucose was associated with increased markers of inflammation and oxidative stress in people within a broad range of glycaemic status[94]. Thus, glycaemic variability might possibly not be fully captured by HbA1c as an indicator of average blood glucose over the previous 2–3 months.

Fasting plasma glucose. Although IGT and IFG are grouped under the umbrella term of prediabetes, their natural history of progression and response to interventions are very different[5]. Relying solely

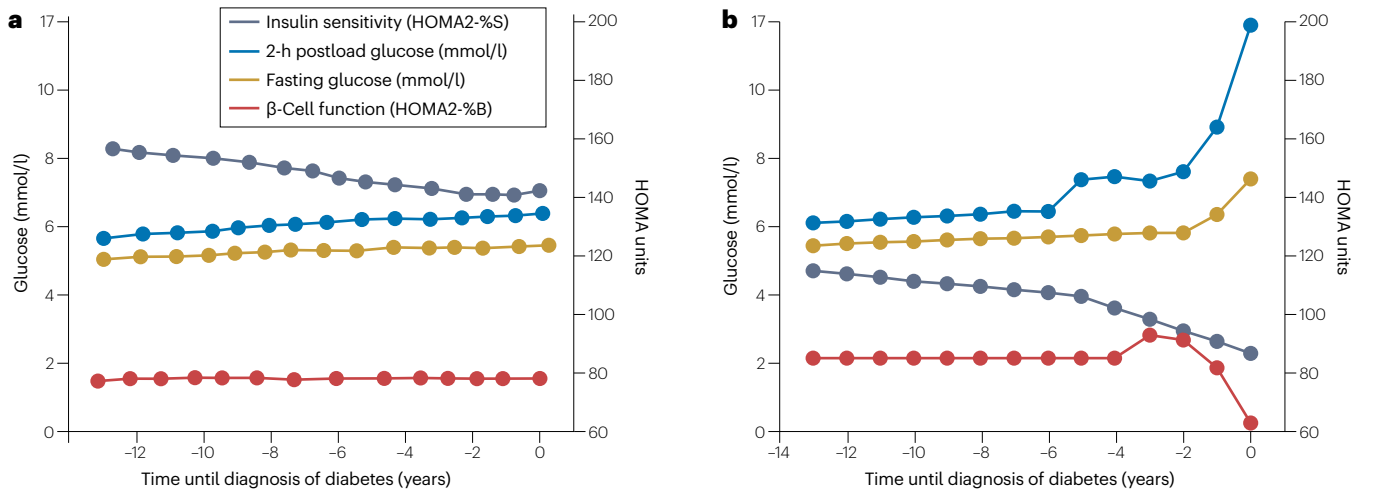

Fig. 3 | Trajectories of glycaemia in the UK Whitehall II study. a, Individuals who did not develop type 2 diabetes mellitus (T2DM). **b**, Individuals who developed T2DM. Individuals who developed T2DM exhibited a decrease in whole-body insulin sensitivity (measured by HOMA-S) up to 10 years prior to the onset of T2DM as well as a steep decline in β-cell function (measured by HOMA-B) closer to the onset of T2DM. Homeostasis Model Assessment (HOMA) is a mathematical method used to quantify insulin resistance and β-cell function, utilizing plasma insulin and glucose levels. Reprinted with permission from ref. 44, Elsevier.

on fasting plasma glucose to diagnose prediabetes would miss a large population of individuals at high risk with isolated IGT, the latter being diagnosed only by 2-h plasma glucose level during OGTT, leading to missed opportunities for early intervention[7].

In addition to its interference with HbA1c assay, G6PD deficiency can confound the accuracy of fasting plasma glucose as a diagnostic test. Many variants in *G6PD* reported in people of non-European descent have been associated with low fasting plasma glucose, reducing the sensitivity of the test[95].

The 2-h plasma glucose during OGTT. Most randomized controlled trials (RCTs) on the prevention of T2DM have used IGT with or without IFG as an inclusion criterion (discussed below)[96]. As per currently accepted definitions, IGT can only be diagnosed by measuring the 2-h post-load plasma glucose during an OGTT, with glucose levels between 7.7 and 11.1 mmol/l (140–199 mg/dl) being considered diagnostic of IGT[2]. Hence, there is a strong rationale for recommending the use of an OGTT for diagnosing prediabetes from a global and low-income and middle-income countries (LMICs) perspective. Apart from the aforementioned limitations of using HbA1c to diagnose prediabetes, OGTT performed by trained non-medical personnel may incur lower costs. By detecting IGT early by employing OGTT, the opportunity for preventing or delaying the onset of T2DM and its progression is high, given the proven benefits of early glycaemic control on reducing long-term microvascular and/or macrovascular complications and all-cause death[97,98].

The 1-h plasma glucose during OGTT. Since the 2010s, there has been a resurgence of interest in the use of the 1-h plasma glucose levels during an OGTT to diagnose prediabetes or even earlier stages of glucose intolerance[99–101]. In a 2024 International Diabetes Federation position paper[102], global experts conducted a comprehensive review of evidence from cohort analyses and intervention studies gathered since the 1980s and recommended the use of 1-h OGTT plasma glucose level ≥8.6 mmol/l (155 mg/dl) to identify individuals at high likelihood of progressing to T2DM. In individuals with normal fasting plasma glucose <5.5 mmol/l (100 mg/dl) and 2-h OGTT plasma glucose level <7.7 mmol/l (140 mg/dl) values, a higher 1-h OGTT plasma glucose level identified those who eventually progressed to prediabetes or T2DM. Elevated 1-h plasma glucose has been suggested to identify individuals likely to progress to T2DM at an earlier stage in the natural history of the disorder than the 2-h plasma glucose. Additionally, using the 1-h rather than 2-h plasma glucose has the potential to shorten the OGTT, with consequent time and cost savings[102].

However, no studies to date have used the 1-h plasma glucose level during OGTT as a criterion for inclusion in intervention studies or tested the efficacy of such interventions in individuals defined by the 1-h plasma glucose. Further research is therefore needed before the 1-h plasma glucose level during OGTT can be recommended for intervention purposes, independent of the 2-h plasma glucose levels. Although using non-fasting 1-h plasma glucose during OGTT to diagnose diabetes and prediabetes seems attractive, both epidemiological and interventional studies are needed to confirm its non-inferiority compared to 2-h plasma glucose during OGTT.

Reproducibilty of OGTT and other screening strategies. In comparison to HbA1c, results of an abnormal OGTT on repeat testing can be inconsistent. However, researchers have reported that individuals with one abnormal OGTT, whether reproducible or not, had a worse cardiovascular risk profile than individuals who had reproducible normal OGTT results[103]. The heterogeneity of fasting plasma glucose, 1-h plasma glucose and 2-h plasma glucose may reflect multiple pathways implicated in glucose sensing, different phases of insulin production and secretion as well as insulin resistance in various target organs, notably liver and muscle, and endogenous glucose production[104]. In a 10-year prospective study involving Chinese individuals of working age, based on receiver operating characteristic analysis, 1-h and 2-h plasma glucose were more predictive than fasting plasma glucose for incident T2DM in people without a family history of young-onset diabetes mellitus. However, in people with a family history of young-onset diabetes

mellitus, fasting plasma glucose was the most robust predictor. This heterogeneity calls for more studies to examine the interactions of these glycaemic parameters with other risk factors, including genetic profiles of individuals to identify people with high lifetime risk of developing diabetes mellitus, especially at younger ages.

Despite the popular use of point-of-care tests for detecting diabetes mellitus or prediabetes, these tests tend to have high specificity but low sensitivity[95,105]. Glycated albumin measurements, such as serum fructosamine, have been used to monitor short-term glycaemic control, for example, during pregnancy, owing to the shorter half-life of serum albumin than blood haemoglobin[106]. However, apart from inaccuracies arising from low albumin states due to poor health or heavy proteinuria, these tests have been shown to have poor correlation with HbA1c[107] even in the presence of normal serum albumin. Although some researchers have advocated using various combinations of fasting plasma glucose, fructosamine or HbA1c to diagnose people with prediabetes or exclude people unlikely to have abnormal 2-h plasma glucose[103,108], the lack of long-term data and standardization of glycated albumin assays limit its utility.

Stepwise diagnosis of prediabetes

The first step in identifying individuals with prediabetes or individuals with undiagnosed T2DM involves the identification of individuals at risk using (wherever data are available) multivariable, non-invasive risk scores, similar to 10-year risk scores for CVD, designed for the population concerned (for example, FINDRISC, Indian Diabetes Risk Score)[109,110] (Fig. 6). With the proviso that the HbA1c assay is reliable without concern of major confounders, fasting plasma glucose and HbA1c along with other cardiometabolic risk factors may be sufficient for risk assessment in individuals at low risk of developing T2DM[111].

However, in some ethnic groups (such as East and South-East Asians, Asian Indians, Native Americans and Pacific Islanders) and in individuals at high risk, for example, those with a family history of T2DM especially for young-onset diabetes mellitus, obesity, gestational diabetes, cardiovascular risk factors, polycystic ovary syndrome and high-risk scores for the aforementioned factors, measuring 2-h plasma glucose during an OGTT is crucial to avoid missing T2DM or IGT, even if fasting plasma glucose and HbA1c values are normal[112].

Additionally, IGT should be confirmed when enrolling individuals in an intensive lifestyle programme or when they are planned to be put on medical treatment for prevention. If the individual is not suitable for such a programme (for example, older adults (>65 years of age) or individuals with frailty) or if such programmes are not available locally or the individual strongly refuses treatment, then OGTT may be omitted. However, most of these individuals at high risk will still benefit from regular OGTT to detect progression. In resource-constrained settings or where opportunistic screening is the only possible method, an additional layer of screening can be added by performing a random capillary blood glucose test with cutoffs for identifying individuals at increased risk of having prediabetes or T2DM (as described for selected populations) prior to an OGTT to minimize the number of OGTTs that needs to be performed[113–116].

The stepped-care approach of using either non-invasive risk scores or capillary blood glucose to identify individuals at high risk who should undergo OGTT for confirmation is particularly relevant to low-resource settings where the cost of the HbA1c assay may be considered unaffordable compared with plasma glucose, leaving aside issues of assay quality. As diabetes risk is not evenly distributed in the population, non-physician workers can be trained to implement simple protocols involving the use of self-assessed risk factors or population-relevant risk scores to identify the 20–30% of individuals at the highest risk of developing T2DM within the next 10 years. These individuals should undergo annual or biannual OGTT with measurement of fasting and 2-h plasma glucose to increase the precision of diagnosis of IGT for effective prevention of diabetes[35,98,117].

Finally, given the proportion of individuals with prediabetes in a particular population, a context-relevant screening strategy with follow-up actions, considering the population characteristics, resource capacity and locally relevant evidence with ongoing evaluation, will provide important insights into the performance of these diagnostic tools to inform policies and practice[118].

Management

The primary aim in the management of prediabetes is to delay or prevent the development of T2DM. Early studies focused on weight loss through lifestyle interventions (comprising dietary

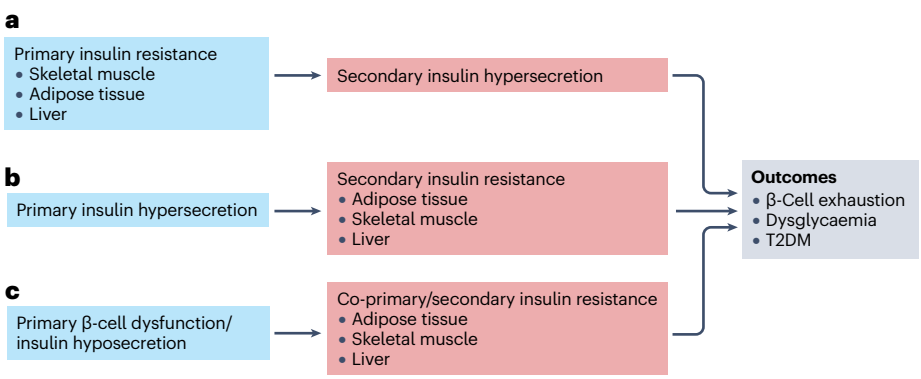

Fig. 4 | Models of β-cell dysfunction in prediabetes and T2DM. a, The most widely accepted model postulates a secondary increase in insulin secretion stimulated by the development of insulin resistance in liver, skeletal muscle and adipose tissue. Prolonged hypersecretion of insulin is followed by β-cell failure and development of dysglycaemia[50]. **b**, An alternative model postulates that the primary event in type 2 diabetes mellitus (T2DM) pathogenesis is increased insulin secretion. The liver, skeletal muscle and adipose tissue reduce their insulin sensitivity in response to chronic hyperinsulinaemia. Over time, β-cell exhaustion occurs and dysglycaemia ensues. **c**, The third model assumes the presence of primary β-cell dysfunction, leading to insulin hyposecretion and dysglycaemia, as might occur in some forms of insulin-deficient diabetes and prediabetes.

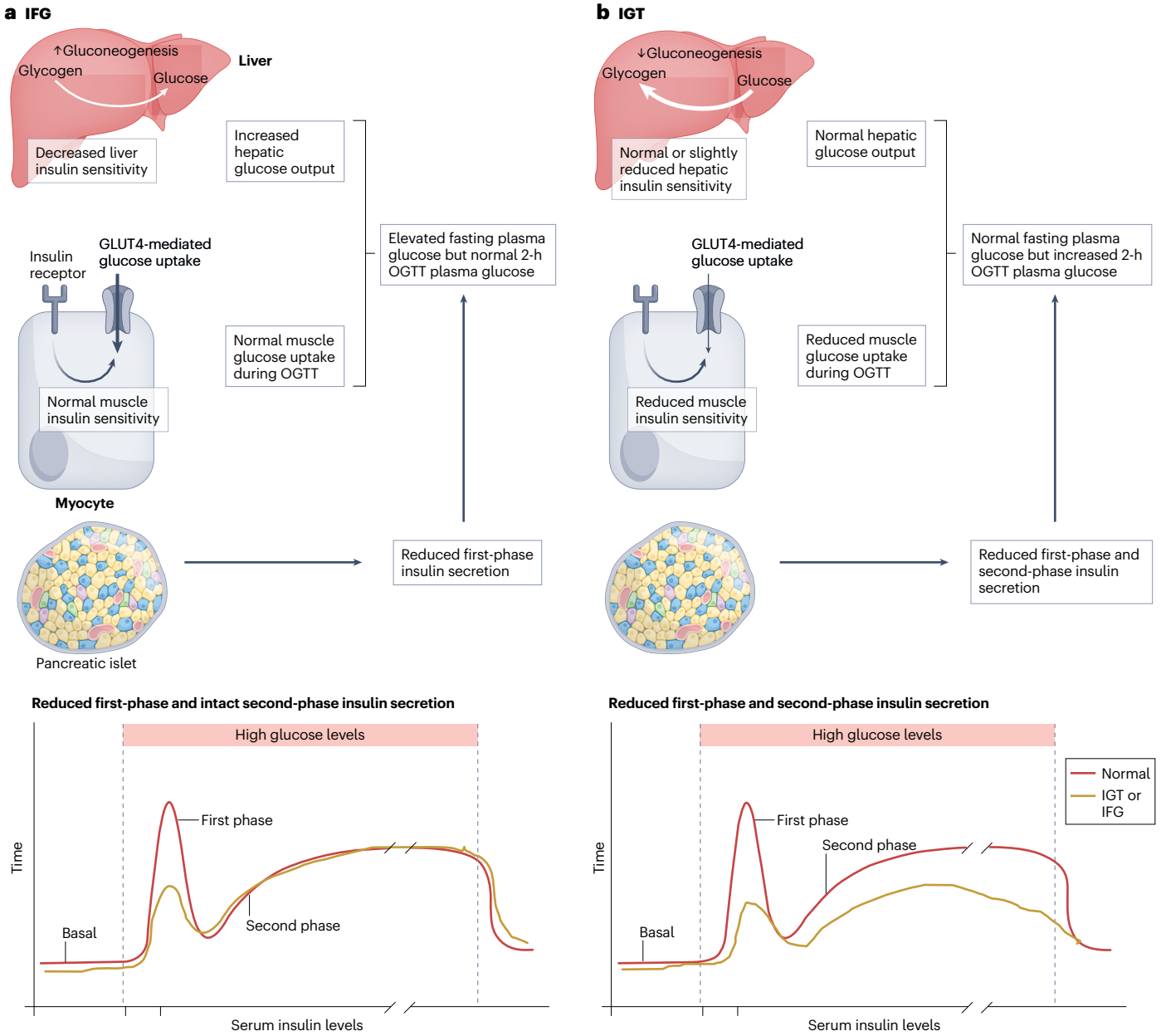

Fig. 5 | Comparison of pathophysiology of IFG and IGT. a, Impaired fasting glucose (IFG) is characterized by reduced hepatic insulin sensitivity and normal skeletal muscle insulin sensitivity, leading to elevated fasting plasma glucose levels (due to increased hepatic glucose output) and normal postprandial (post-load) glucose levels due to unimpaired uptake of glucose into skeletal muscle. Furthermore, there is diminution of the first phase of insulin secretion and intact second-phase insulin secretion. **b**, Impaired glucose tolerance (IGT) is characterized by normal (or slightly decreased) hepatic insulin sensitivity but a profound decrease in sensitivity of skeletal muscle to insulin. This alteration leads to normal fasting plasma glucose levels but elevated post-load (postprandial) levels owing to reduced uptake of glucose into skeletal muscle. Both first-phase and second-phase insulin secretion are impaired[6]. GLUT4, glucose transporter 4; OGTT, oral glucose tolerance test.

modifications and increased physical activity) or the addition of metformin[119–121]. Since the 2010s, studies have demonstrated that newer weight-reducing medications, such as GLP1 receptor agonists and GLP1–GIP receptor agonists, and metabolic surgery could also slow the progression of prediabetes and/or induce its regression[122] (Box 2).

Lifestyle interventions

Several major RCTs, including the China Da Qing Study[120], the Finnish Diabetes Prevention Study (DPS)[121], the United States Diabetes Prevention Program (US-DPP)[119] and Indian DPP[123], have reported the benefits of lifestyle interventions on preventing T2DM in individuals with IGT[119–121,123–130] (Table 2). In most of these trials, the benefit was

primarily attributable to weight loss, although, in some populations, the weight loss was only modest. The baseline BMI was lower in the Chinese and Indian study populations than in the American and Finnish groups (Table 2). Of note, none of these studies used HbA1c to define prediabetes and only included participants with isolated IGT, or IGT plus IFG, but not isolated IFG.

In the US-DPP, individuals with IGT were randomized to intensive lifestyle intervention, metformin or usual care consisting of standard lifestyle modification (with a troglitazone arm discontinued due to safety concerns)[120]. The lifestyle intervention group received 16-week sessions focusing on weight loss through dietary changes and increased physical activity with pre-specified glycaemic and BMI criteria and ongoing support. After 3 years, lifestyle intervention was more effective than metformin in reducing diabetes incidence (Table 2). In the Finnish DPS, the intervention group received structured lifestyle intervention (diet and exercise) and lost weight, with a reduced incidence of T2DM[121]. In the Chinese Da Qing Study, individuals with IGT who received lifestyle intervention using diet only, exercise only or both also had a reduced incidence of T2DM[120] (Table 2).

In addition, long-term follow-up reinforced these benefits. In the Finnish DPS, a 7-year analysis showed a sustained 43% reduction in progression to T2DM compared with non-intervention[131]. In the China Da Qing cohort, a 20-year follow-up showed a 41% reduction in risk for cardiovascular mortality, 29% reduction in all-cause mortality, and 45% reduction in the incidence of T2DM[132]. At 30 years, the intervention group maintained a 33% lower cardiovascular mortality, 26% lower all-cause mortality, 39% lower T2DM incidence and a 35% lower incidence of microvascular complications than the non-intervention group. The reduced risk of microvascular complications was driven primarily by a 40% reduction in retinopathy, whereas rates of diabetic nephropathy and neuropathy were not significantly lower than in the non-intervention group[132].

The DPP Outcomes Study (DPPOS)[97], a long-term follow-up of the US-DPP, confirmed that both lifestyle intervention and metformin delayed T2DM onset, although the differences between groups narrowed over time. At 15 years, incidence of T2DM was reduced by 27% with lifestyle intervention and by 18% with metformin. At 21 years, no significant differences in major cardiovascular events were observed across groups. However, participants who did not progress to T2DM had a 28% lower prevalence of aggregate microvascular complications than participants who developed T2DM. Although no significant differences in microvascular outcomes were observed between treatment arms overall, a subgroup analysis of women found lifestyle intervention was associated with a 21% lower prevalence of microvascular complications than the placebo group and with a 22% lower prevalence than the metformin group. The widespread use of statins, blood pressure-lowering agents and group-based lifestyle interventions in the post-trial period might have attenuated the benefits of intervention[133].

Isolated IFG. Most studies on lifestyle interventions have focused on individuals with IGT or IGT plus IFG. In 2023, a meta-analysis[96] examined four trials including people with isolated IFG, isolated IGT or both[124,128–130]. Although lifestyle interventions effectively reduced diabetes risk in those with IGT, no clear benefit was observed in individuals with isolated IFG[96], suggesting that structured programmes in individuals with isolated IFG might not be cost-effective (Fig. 7).

The explanation for the relative lack of response to intensive lifestyle intervention in individuals with isolated IFG is unclear and may be related to differences in the pathophysiology of isolated IGT and isolated IFG. Abnormal glucose sensing, impaired suppression of glycogenolysis or excessive glucose uptake with reduced efficiency of glycogen synthesis may underlie the pathogenesis of isolated IFG[6]. Many individuals with isolated IFG also exhibit features of metabolic syndrome with insulin resistance owing to excess and/or ectopic adipose tissue, notably increased hepatic lipid mass. In these individuals, greater caloric deficit may be needed to reduce body weight to reduce the progression from isolated IFG to T2DM[92]. Of note, several studies have shown that many individuals with isolated IFG may spontaneously return to normoglycaemia[134]. On the other hand, isolated IGT is increasingly associated with insulin resistance in skeletal muscles along with reduced β-cell function[6,62]. Hence, exercise training to reduce muscle insulin resistance and use of metformin to increase postprandial insulin secretion may be more effective in IGT than IFG. Another, as-yet unexplored, explanation is the possibility that individuals with isolated IFG are less enthusiastic about complying with their prescribed lifestyle change. There are well-documented differences in the age and sex profiles of IFG and IGT[6]. Although there was a clear relationship between age and increasing prevalence of IGT, the prevalence of IFG was similar in all age groups[5]. Given the greater health awareness in

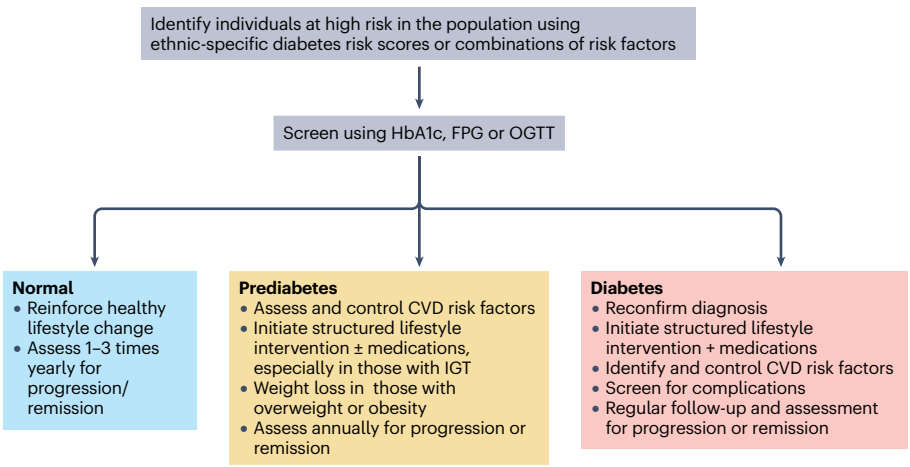
Identify individuals at high risk in the population using ethnic-specific diabetes risk scores or combinations of risk factors
Screen using HbA1c, FPG or OGTT
Normal
• Reinforce healthy lifestyle change
• Assess 1–3 times yearly for progression/ remission
Prediabetes
• Assess and control CVD risk factors
• Initiate structured lifestyle intervention ± medications, especially in those with IGT
• Weight loss in those with overweight or obesity
• Assess annually for progression or remission
Diabetes
• Reconfirm diagnosis
• Initiate structured lifestyle intervention + medications
• Identify and control CVD risk factors
• Screen for complications
• Regular follow-up and assessment for progression or remission

Fig. 6 | Stepped-care approach to diagnosis and management of prediabetes. The stepped-care approach to diagnosing prediabetes utilizes identification of individuals at high risk in the population as the first step, which is followed by screening using glycated haemoglobin (HbA1c), fasting plasma glucose (FPG) or the oral glucose tolerance test (OGTT). The choice of test depends on the characteristics of the population being screened. In certain ethnic groups or individuals deemed to be at high risk or in those who are likely to be entered into an intensive lifestyle programme, the diagnosis of prediabetes should utilize a 2-h post-load plasma glucose value during OGTT and not depend on FPG or HbA1c alone. CVD, cardiovascular disease; IGT, impaired glucose tolerance.

Box 2 | Remission of prediabetes

Traditionally, remission is considered in the context of overt type 2 diabetes mellitus (T2DM). However, attempting remission at the stage of prediabetes is plausible as β-cell function might be better preserved at this stage before T2DM sets in.

A subset of individuals with prediabetes may spontaneously revert to normoglycaemia even in the absence of interventions[10,134,219]. Although this phenomenon does not compromise the benefits of T2DM prevention in the setting of randomized controlled clinical trials, the heterogeneity in progression from prediabetes to T2DM should be considered when deciding on the most appropriate course of action. Lifestyle improvements are beneficial across various health conditions and should be promoted irrespective of glycaemia. Likewise, addressing cardiovascular risk factors, such as hypertension and dyslipidaemia, according to local guidelines is crucial. In a comprehensive Cochrane review encompassing 103 prospective cohort studies on prediabetes, 47 studies reported rates of conversion to normoglycaemia[10]. Within these cohorts, regression rates to normoglycaemia ranged from 33% to 59% over 1–5 years, decreasing to 17–42% for studies with 6–11 years of follow-up. The risk of progression to T2DM and the regression to normoglycaemia exhibited variability across studies, partly due to lack of response to lifestyle intervention and differences in definitions of prediabetes subtypes as well as adherence and response to interventions.

older adults, individuals with IGT may be more likely to engage with, and respond to, lifestyle advice.

From a population perspective, filling intervention programmes with people with isolated IFG may not have a major impact on the risk of T2DM. As far as individuals with IFG are concerned, encouraging them to adopt healthy lifestyles might be sufficient with a focus on controlling other risk factors such as high blood pressure to reduce risk of CVD. Thus, an OGTT should be used to screen individuals with IGT for entry into structured T2DM prevention programmes whereas further research is needed to identify interventions for delaying the progression of isolated IFG to T2DM.

Pharmacological interventions

Several placebo-controlled RCTs have evaluated various drugs[119,123,127,135–150] (Table 3), including metformin[97,150], troglitazone[135,143], acarbose[136,140], orlistat[148], pioglitazone[137], rosiglitazone[138,150], ramipril[139], voglibose[142], nateglinide[145], valsartan[146] and liraglutide[144,147], for the prevention of progression of prediabetes to T2DM. Although some trials have shown favourable outcomes, it should be remembered that prediabetes is not universally accepted as a disease. In this regard, pharmacological or surgical interventions remain unapproved in many countries and cost-effectiveness remains uncertain.

Metformin. Although metformin was shown to prevent the progression to T2DM, the FDA has not approved its use in clinics and it is currently used off-label in the USA and other countries for this indication[151]. In the US-DPP and DPPOS, the efficacy of metformin varied, being greater in individuals with BMI ≥35 kg/m^2, individuals with IGT plus elevated fasting plasma glucose, individuals <45 years of age, African-Americans[152] and women with prior gestational diabetes[97,153,154]. When HbA1c was used to define incident diabetes, metformin and lifestyle modification had similar efficacy, with no age-related associations[155].

In the China-DPP, which included individuals with IGT and IFG[156], most had IGT. Metformin plus lifestyle intervention was more effective than lifestyle intervention alone, particularly in men, younger individuals and those with higher BMI. On subgroup analysis, only patients in the IGT group demonstrated a reduction in T2DM incidence with a hazard ratio of 0.83 (95% CI 0.69–0.99).

In the US-DPP, a short 'washout' period was implemented to evaluate the persistence of the effects of metformin after discontinuation[157]. The study found that, upon stopping metformin, the incidence of T2DM increased, suggesting that much of its benefit was pharmacological and did not persist upon withdrawal. Nevertheless, even after the washout, the intervention group still showed a 24.9% reduction in incident T2DM. The duration of post-discontinuation effect of metformin remains unclear; however, in a small study of 20 individuals with IGT treated with metformin versus 20 individuals receiving placebo, metformin led to improved glucose tolerance that persisted for up to 6 months after the drug was stopped[158].

The American Diabetes Association recommends considering metformin for T2DM prevention in adults at high risk, including in those with IGT (ages 25–59 years, BMI >35 kg/m^2), elevated fasting plasma glucose (≥6.1 mmol/l (110 mg/dl)), high HbA1c (≥42 mmol/mol (6.0%)), and a history of gestational diabetes, based on evidence from US-DPP[159].

Metformin remains an inexpensive, widely available and cost-effective intervention for diabetes mellitus prevention in individuals at high risk with prediabetes[160]. Although actual costs vary by pharmacy and insurance coverage, the American Diabetes Association reports that the median National Average Drug Acquisition Cost for a 30-day supply of 500 mg generic immediate-release metformin is approximately US$1, whereas the average wholesale price is around US$87 (ref. 161). In a DPP cost-effectiveness analysis, the 10-year cumulative direct medical cost of metformin was approximately US$2,300 per person[162]. Although detailed evaluations of out-of-pocket costs for metformin in prediabetes are limited, generic formulations are generally low-cost, although individual expenses may vary substantially based on insurance and access.

Thiazolidinediones. In the US-DPP, troglitazone was used as an early intervention and was found to be effective in T2DM prevention; however, troglitazone was discontinued owing to liver toxicity[143] (Table 3). The Troglitazone in Prevention of Diabetes (TRIPOD)[163] study in Hispanic women with prior gestational diabetes showed >50% risk reduction in the incidence of T2DM but was terminated early when the drug was withdrawn. The Pioglitazone In Prevention Of Diabetes (PIPOD) Study[164], a follow-up to TRIPOD study, found that pioglitazone preserved β-cell function, halted the decline observed in the TRIPOD placebo group and maintained the stability in β-cell function as observed with troglitazone. The Actos Now for the prevention of diabetes (ACT NOW) trial[137,165] found that pioglitazone was associated with lower diabetes incidence and higher conversion to normal glucose tolerance than placebo (Table 3). In the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) trial, rosiglitazone was associated with lower diabetes incidence than placebo[138]. In the Canadian Normoglycaemia Outcomes Evaluation, reversion to normoglycaemia was more frequent in the metformin plus rosiglitazone group than in the placebo group[150]. On the other hand, in the Beijing Prediabetes Reversion Program (BPRP), pioglitazone was no different

Table 2 | Summary of trials of lifestyle intervention in prediabetes

Study; country; study years	Prediabetes definition	Age (mean±s.d.); baseline BMI (kg/m^2) (mean±s.d.)	Study groups (number of participants)	Weight loss target	Mean follow-up; duration of post-intervention follow-up	Reversal of prediabetes	Relative risk reduction for T2DM	Absolute risk reduction for T2DM	Ref.
Da Qing; China; 1986–1992	IGT	45±9 years; 25.8±3.8	Diet (130), exercise (141), combined diet and exercise (126), control (133)	NA	6 years; 30 years	NR	Diet: 31.5%, exercise: 46%, diet and exercise: 42%	65.9% in control vs 47.1% in diet, 44.2% in exercise, and 44.6% in diet and exercise groups	120
Finnish DPS; Finland; 1993–2001	IGT	55±7 years; 31±4.5	Combined diet and exercise (265), control (257)	>5%	4 years; 13 years	NR	Diet and exercise: 58%	32 cases in diet and exercise vs 78 in control[a]	121
DPP; USA; 1996–2001	IGT (plus IFG in some)	51±10.7 years; 34±6.7	Combined diet and exercise (1,079), metformin (1,073), control (1,082)	7%	2.8 years; 15 years	Lifestyle: 40%, metformin: 20%	Diet and exercise: 58%, metformin: 31%	10.8% in placebo vs 7.8% in metformin and 4.8% in lifestyle groups[b]	119
Japanese Trial; Japan; 1984–2003	IGT (men only)	NR; 24±2.2	Combined diet and exercise (102), control (356)	NS	4 years; NR	Lifestyle: 53.8%	Diet and exercise: 67.4%	9.3% in control vs 3.0% in intervention	125
Indian DPP-1; India; 2003–2005	IGT	46±5.7 years; 25.8±3.5	Diet and exercise (133), metformin (133), diet, exercise and metformin (136), control (136)	NS	3 years; NR	NR	Diet and exercise: 28.5%, metformin: 26.4%, diet, exercise and metformin: 28.2%	55.0% in control vs 39.3% in diet and exercise, 40.5% in metformin, and 39.5% in diet, exercise, and metformin groups[c]	123
Indian DPP-2; India; 2003–2005	IGT	45±6.2 years; 26±3.3	Diet and exercise (203), diet, exercise and pioglitazone (204)	NS	3 years; NR	Lifestyle: 32.3%, pioglitazone: 40.9%	Diet, exercise and pioglitazone: 1.8%	31.6% in diet and exercise vs 29.8% in pioglitazone[c]	127
D-CLIP; India; 2010–2013	Isolated IGT, isolated IFG, IFG and IGT	44.9± 9.3 years; 27.9±3.3	Control (133), diet and exercise (265)	NS	6 months; 3 years	–	32%	34.9% in control vs 25.7% in intervention group[c]	130
K-DPP; India; NS	Prediabetes (individuals at high risk based on IDRS)	30–60 years; NS	Control (507), structured lifestyle advice (500)	NS	2 years; 2 years	NS	12% (non-significant)	17.1% in control vs 14.9% in intervention group	129
LPD; UK; NS	Prediabetes (IGT and/or IFG)	64 years; NS	Intervention group (structured education programme) (447) and standard-care group (433)	NS	3 years; 3 years	NS	~26% (non-significant)	NS	119
ZSPLD; Japan; 2003	IFG	30–60 years; 24	Frequent intervention group (311), control (330)	NS	3 years; NS	NS	44%	4.4%	128
PROP-ABC Study; USA; 2006–2012	Incident prediabetes during follow-up	53.3± 9.28 years; 30.6±6.70	223 (72 controls+ 138 lifestyle intervention)	NS	5 years; NR	42.8% (reverted to NGR)	50%	NR	210
China-DPP	IGT and IFG	53 years (IQR 45–59 years); 26.28±2.84	Lifestyle (847), lifestyle and metformin (831)	NS	2 years; NS	NR	Lifestyle and metformin: 17%	17.27% in the lifestyle plus metformin group vs 19.83% in the lifestyle group	156

D-CLIP, Diabetes, a Community Lifestyle Intervention Program; DPP, Diabetes Prevention Program; DPS, Diabetes Prevention Study; IDRS, Indian Diabetes Risk Score; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IQR, interquartile range; K-DPP, Kerala Diabetes Prevention Program; LPD, Let's Prevent Diabetes; NA, not applicable; NGR, normal glucose regulation; NR, not reported; NS, not specified; PROP-ABC, Pathobiology and Reversibility of Prediabetes in a Biracial Cohort; T2DM, type 2 diabetes mellitus; ZSPLD, Zensharen Study for Prevention of Lifestyle Diseases. [a]Incidence per 100 person-years. [b]Incidence per 100 person-years. [c]Cumulative incidence.

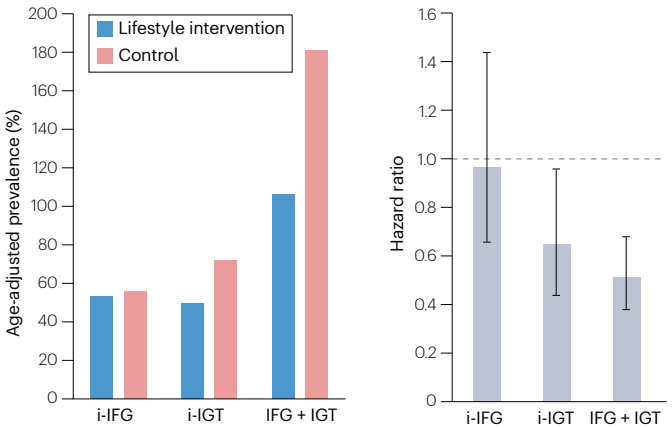

Fig. 7 | Effect of lifestyle intervention on type 2 diabetes mellitus incidence and risk according to prediabetes phenotype. Incidence of diabetes (left panel) according to prediabetes phenotype and use of classical lifestyle intervention, and effect of lifestyle intervention (right panel) on risk of developing diabetes, according to prediabetes phenotype[96]. i-IFG, isolated impaired fasting glucose; i-IGT, isolated impaired glucose tolerance; IFG + IGT, impaired fasting glucose and impaired glucose tolerance. Error bars are 95% confidence intervals.

from lifestyle intervention in terms of normoglycaemia reversion, suggesting inter-ethnic differences in treatment responses[166].

α-Glucosidase inhibitors. In the Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM) trial[136], the acarbose group demonstrated a lower incidence of T2DM than the placebo group. Similarly, the China Acarbose Cardiovascular Evaluation (ACE) study[140] found that acarbose not only reduced diabetes mellitus progression but also increased regression to normoglycaemia in individuals with IGT. A Japanese study reported a similar trend with voglibose[142]. Post-hoc analyses of findings from the STOP-NIDDM trial suggested that acarbose might provide cardiovascular benefits in individuals with IGT[167].

SGLT2 inhibitors. Post-hoc analyses of RCTs that assessed the organ-protective effects of SGLT2 inhibitors (such as dapagliflozin and empagliflozin) in individuals with heart failure or CKD suggested that these drugs might prevent new-onset T2DM, although results were inconsistent[168–170]. Of note, these cardiovascular outcome trials did not specifically include individuals at high risk of diabetes mellitus, which is in contrast to prevention trials using metformin and thiazolidinediones.

In a pooled analysis of the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) and Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trials, dapagliflozin was associated with reduced risk of incident T2DM[168]. The authors suggested that, apart from weight loss with SGLT2 inhibitors, reduction in insulin resistance and improved β-cell function might also contribute to this benefit[168].

However, in the Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction (EMPEROR-Preserved), which recruited participants with heart failure and without diabetes mellitus, empagliflozin did not reduce incident diabetes mellitus compared with placebo[169]. Similar results were reported in the Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Reduced Ejection Fraction (EMPEROR-Reduced)[170].

GLP1 receptor agonists and GLP1–GIP receptor agonists. In major RCTs, the use of GLP1 receptor agonists and dual GLP1–GIP receptor agonists to promote weight loss had a significant impact on the progression of prediabetes (Table 3). In the Satiety and Clinical Adiposity – Liraglutide Evidence (SCALE) study, which examined the effects of liraglutide in people with obesity and prediabetes, the progression from prediabetes to diabetes mellitus was more effectively slowed down in the treatment group than in the placebo group[147].

The Semaglutide Treatment Effect in People with Obesity-1 (STEP-1) study evaluated the efficacy of semaglutide on weight loss in adults with overweight or obesity without diabetes mellitus[149]. Reversion to normoglycaemia was significantly more frequent in the semaglutide group than in the placebo group. In the STEP-10 trial involving 207 individuals with obesity with prediabetes, semaglutide increased the odds of regression to normoglycaemia compared with placebo[171].

The dual GLP1–GIP receptor agonist tirzepatide was evaluated in 2,539 individuals with overweight or obesity without diabetes mellitus, 1,032 of whom had prediabetes[141]. At the end of 3 years of follow-up, progression to T2DM occurred significantly less frequently in participants randomized to tirzepatide than in those randomized to placebo. Reversion to normoglycaemia was also more frequent in those who received tirzepatide than in those receiving placebo. This study and other RCTs support the hypothesis that the weight-reducing effects of tirzepatide reduce the risk of T2DM, CVD, CKD and MASLD[172].

A systematic review and meta-analysis evaluated the effects of GLP1 receptor agonists in eight RCTs (liraglutide in six, exenatide and semaglutide in one each). All these RCTs enrolled individuals with prediabetes (based on HbA1c or OGTT)[173]. Five of these studies indicated that GLP1 receptor agonists increased the likelihood of regression from prediabetes to normoglycaemia compared with placebo (OR 4.56, CI 3.58–5.80). In three studies, the GLP1 receptor agonist group had lower odds of developing T2DM than the placebo group (OR 0.31, CI 0.12–0.81).

Despite these promising results confirmed in closely supervised RCT settings, the weight loss effects were lost with treatment discontinuation. Given their high costs, the cost-effectiveness of GLP1 receptor agonists, dual GLP1–GIP receptor agonists and other anti-obesity drugs in the pipeline for prevention and treatment of diabetes remains a contentious issue[174]. Other experts suggested that short-term use of these weight management drugs with boosters may form part of a multi-component strategy including lifestyle modification and dietary changes, although the potential adverse effects of weight cycling should not be overlooked. Given the strong behavioural component of obesity and the costs involved in long-term pharmacotherapy, using medications as the sole strategy to reduce body weight and prevent diabetes mellitus and its comorbidities is unlikely to be affordable, sustainable or accessible. Instead of 'preventing' diabetes mellitus, these drugs may merely be 'treating' the condition earlier.

Vitamin D

Empirical vitamin D supplementation may help reduce the risk of progression to T2DM in adults with prediabetes. A pooled analysis of three RCTs demonstrated that vitamin D supplementation not only delayed progression to T2DM but also increased the likelihood of regression to normoglycaemia by 30% compared with placebo[175]. In intention-to-treat analyses, vitamin D reduced the risk of incident T2DM by 12% (unadjusted) and 15% (adjusted)[175]. These trials enrolled 4,190 adults (≥18 years of age) with prediabetes who received oral vitamin D supplementation for at least 2 years. Interventions included cholecalciferol (vitamin D3) in the Tromsø study[176] and the D2d study[177], and eldecalcitol (a synthetic

analogue of calcitriol) in the DPVD study[178]. Although the optimal formulation of vitamin D remains to be determined, the mean baseline serum 25-hydroxyvitamin D levels among participants was 63 nmol/l (25 ng/ml). These studies found that sustained higher 25-hydroxyvitamin D levels conferred progressively reduced risk for diabetes mellitus than lower endogenous 25-hydroxyvitamin D levels. However, a precise target level to optimally reduce T2DM risk has not yet been established. Another systematic review of 11 trials, with baseline mean 25-hydroxyvitamin D levels ranging from 12 to 28 ng/ml (30–70 nmol/l), also found that vitamin D supplementation was associated with a reduced risk of incident T2DM, with a relative risk of 0.90 (95% CI 0.81–1.00)[179].

Given its low cost, favourable safety profile and potential to reduce diabetes mellitus risk, empirical vitamin D supplementation might be a reasonable consideration for adults with prediabetes.

Metabolic surgery

As of now, metabolic (bariatric) surgery is the most effective treatment for obesity and is often considered in people who are not suitable for,

Table 3 | Summary of trials of pharmacological interventions for prediabetes

Study; country; year	Prediabetes phenotype	Baseline BMI mean (kg/m^2) (s.d.); study size	Mean follow-up	Study groups	Relative risk reduction for T2DM (95% CI)	Absolute risk reduction for T2DM	Refs.
TRIPOD; USA; 2002	IGT (women with history of gestational diabetes)	30 (5.7); 266	2.5 years	Troglitazone vs placebo	55% (17–75)	12.1% vs 5.4%	135
STOP-NIDDM; multinational; 2002	IGT and IFG	31 (4.2); 1,429	3.3 years	Acarbose vs placebo	25% (10–37)	42% vs 32%	136
DPP; USA; 2002	IGT and IFG	34 (6.7); 3,234	2.8 years	Metformin vs placebo	31% (17–43)	11.0% vs 7.8%	119
DPP; USA; 2005	IGT	NR; 585	0.9 years	Troglitazone vs placebo	75% (NR)	3.0% vs 12.0%	143
XENDOS; multinational; 2006	Normal glucose regulation and IGT	37 (4.4); 3,305	4 years	Orlistat vs placebo	37% (14–54)	9% vs 6.2%	148
Indian DPP-1; India; 2006	IGT	25.8 (3.5); 531	2.5 years	Metformin vs placebo	26.4% (19.1–35.1)	55.0% vs 40.5%	123
Indian DPP-2; India; 2006	IGT	25.9 (3.3); 407	3 years	Pioglitazone vs placebo	2% (–44 to 33)	31.6% vs 29.8%	127
DREAM; multinational; 2006	IGT and IFG	30.9 (5.6); 5,269	3 years	Rosiglitazone vs placebo	62% (56–67)	25.0% vs 10.6%	138
DREAM; multinational; 2006	IGT and IFG	30.9 (5.6); 5,269	3 years	Ramipril vs placebo	9% (–3 to 20)	19.5% vs 18.1%	139
Voglibose Trial; Japan; 2006	IGT	25.8 (3.8); 1,780	0.9 years	Voglibose vs placebo	40% (18–57)	17% vs 8%	142
NAVIGATOR; multinational; 2010	IGT and IFG	30.5 (5.4); 9,306	5 years	Nateglinide vs placebo	−7% (−15 to 0)	34% vs 34%	145
NAVIGATOR; multinational; 2010	IGT and IFG	30.5 (5.4); 9,306	5 years	Valsartan vs placebo	14% (8–20)	36.8% vs 33.1%	146
ACT NOW; USA; 2010	IGT	33.7 (s.e. 0.4); 602	2.4 years	Pioglitazone vs placebo	72% (51–84)	7.6% vs 2.1%	137
CANOE; Canada; 2010	IGT	31.7 (27.1–36.8); 207	3.9 years	Metformin and rosiglitazone vs placebo	66% (41–80)	39% vs 14%	150
ACE; China and Hong Kong; 2010	IGT	24.5 (3.1); 6,522	5 years	Acarbose vs placebo	18% (6–29)	3.8% vs 3.2%	140
SCALE; multinational; 2010	IGT and IFG	38.9 (6.4); 2,254	3 years	Liraglutide vs placebo	79% (66–87)	6% vs 2%	144,147
STEP-I; multinational; 2021	HbA1c <6.4	>30; 1,961	1.3 years	Semaglutide	NA	Regression to normoglycaemia: 84.1% vs 47.8%	149
SURMOUNT; multinational; 2025	(2 of 3 criteria HbA1c, fasting plasma glucose, OGTT)	38.8 (7.1); 2,539 (1,032 with prediabetes)	3 years	Tirzepatide vs placebo	NR	13.3% vs 1.3%	141

ACE, Acarbose Cardiovascular Evaluation; ACT NOW, Actos Now for the prevention of diabetes; CANOE, Canadian Normoglycemia Outcomes Evaluation; DPP, Diabetes Prevention Program; DREAM, Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication; HbA1c, glycated haemoglobin; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NA, not available; NAVIGATOR, Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research; NR, not reported; OGTT, oral glucose tolerance test; SCALE, Satiety and Clinical Adiposity – Liraglutide Evidence; STEP-I, Semaglutide Treatment Effect in People with Obesity; STOP-NIDDM, Study to Prevent Non-Insulin Dependent Diabetes Mellitus; T2DM, type 2 diabetes mellitus; TRIPOD, Troglitazone in the Prevention of Diabetes; XENDOS, XENical in the prevention of Diabetes in Obese Subjects.

refuse or fail pharmacotherapy[180]. Individuals with prediabetes who underwent metabolic surgery had a high likelihood of return to normoglycaemia with reduced risk of progressing to T2DM[181,182] albeit with differences in success rates depending on the type of surgery[183].

In a 4-year retrospective observational study including 669 individuals with obesity and prediabetes (defined as HbA1c ≥5.7% and <6.5%) who underwent metabolic surgery[181], the respective remission rates of prediabetes, that is, return to normoglycaemia, were 82%, 73%, 66% and 58% in the first, second, third and fourth years, respectively. Older patients (49–67 years of age) had lower odds of prediabetes remission from the third year of follow-up than younger patients (19–38 years of age).

In a study in the USA that compared the effects of metabolic surgery versus usual care on the incidence of T2DM in individuals with obesity aged 21–65 years[184], 3,060 met criteria for prediabetes at baseline. The usual-care group had a relative risk of progressing to T2DM of 33.7 at 1 year (95% CI 13.8–82.2) and 138.8 at 3 years (95% CI 19.3–992.7) compared with the surgical group.

Long-term studies also support the cost-effectiveness of metabolic surgery compared with lifestyle intervention and medications. This is mainly due to sustained effects on weight loss with avoidance of escalating treatment and drug costs. Progression rates to T2DM were lower 5 years postoperatively in patients who lost >25% of their baseline weight than in those who lost <15% of their weight during the first postoperative year (4.7% versus 14.0%; P <0.001)[185]. This progression was independent of baseline weight, age and sex.

National programmes for T2DM prevention

Given the large body of evidence supporting the preventable nature of T2DM in those with prediabetes, particularly in those with IGT, there is justification to translate this evidence into national diabetes prevention programmes to reduce the burden of T2DM and its complications, notably CVD[35]. However, only a few countries have implemented these large-scale prevention programmes.

The Centres for Disease Control National Diabetes Prevention Program (National DPP), implemented in the USA since 2012, focuses on structured lifestyle interventions targeting weight loss and increased physical activity[186]. This programme has demonstrated remarkable success in reducing the incidence of T2DM among adults with prediabetes. In one study from the University of Michigan, participants (median 18 sessions attended) had significantly improved BMI, triglyceride levels and HbA1c at 1 and 2 years, with a 40% lower odds of developing T2DM at 1 year and 20% lower odds at 2 years than non-participants[187]. Another analysis showed that T2DM incidence decreased with increased programme attendance — 14.0% in non-attendees, 12.8% with some attendance and 7.5% in those who attended four or more sessions[188]. Overall, the National DPP has demonstrated efficacy in improving weight, physical activity and metabolic parameters, concomitantly lowering T2DM risk.

The English National Health Service Diabetes Prevention Programme (NHSDPP), one of the largest behaviour-change initiatives, used HbA1c or fasting plasma glucose to identify individuals with prediabetes and offered 13 group sessions of intensive lifestyle intervention over 9 or 12 months. Referral to the NHSDPP was associated with a 20% reduced risk of progression to T2DM (adjusted HR 0.80, 95% CI 0.73–0.87), and the probability of remaining free of T2DM at 36 months was 87.3% among referred individuals versus 84.6% in those not referred[189]. Further analysis showed that attending at least 7 of the 13 sessions was linked to a 45.5% decreased risk of developing T2DM (HR 0.545, 95% CI 0.455–0.652)[190].

In a population-based simulation model that replicated prediabetes trends in the population of the USA from 1997 to 2010, the efficacy of three lifestyle intervention strategies, namely, the DPP, DPP-YMCA and HELP-DP, over the course of 5, 10 and 15 years were evaluated[191]. The simulated impacts of these programmes demonstrated reduced incidence of T2DM and premature mortality. In this simulation model, lifestyle intervention, if sustained for 1 year, could reduce T2DM incidence over 15 years.

Taken together, a multipronged approach including population-based interventions (for example, sugar taxes), targeted treatment in individuals at high risk and creating a health-enabling environment, including reduced pollution, improving health literacy, and closing social and health disparities, are important societal–community–personal strategies to reduce the burden of obesity, prediabetes, T2DM and non-communicable diseases[35].

Quality of life

Although lifestyle interventions are effective in preventing or delaying T2DM, sustaining long-term adherence remains a major challenge[192]. Although metabolic surgery is a highly effective preventive option, many individuals are reluctant to consider it[193]. Pharmacological therapies, particularly newer agents such as GLP1 receptor agonists and dual GLP1–GIP receptor agonists, offer promising alternatives by promoting substantial weight loss, improving insulin sensitivity and providing additional benefits such as MASLD resolution[172] and improving symptoms of depression[194]. Studies assessing the direct impact of T2DM prevention on quality of life have consistently shown improvements linked to better glucose control, weight reduction and other metabolic factors[195]. For example, participants in the US-DPP intervention group experienced modest but significant improvements in quality-of-life measures[196].

Cost-effectiveness

Economic evaluations support the value of T2DM prevention strategies. In the US-DPP, lifestyle intervention was cost-saving for adults <45 years of age and remained cost-effective across older age groups (>65 years of age)[197]. Metformin use was cost-effective in individuals <65 years of age but not in older adults due to reduced efficacy[198]. A 10-year cost-effectiveness analysis of the US-DPP and its follow-up (DPPOS) showed that diabetes mellitus prevention programmes improved quality of life with minimal or no additional cost[153]. In a real-world study of 7,846 adults with prediabetes and employer-sponsored insurance, only 753 (9.6%) enrolled in the National DPP between 2015 and 2019 (ref. 199). Compared with non-enrollees, direct medical costs were reduced by approximately US$4,600 per enrollee over 2 years — driven by decreased hospitalization (US$3,000), outpatient (US$1,200) and emergency visit costs (US$300). These findings support the broader adoption of structured prevention programmes.

Global implementation and disparities

Implementation of T2DM prevention strategies in LMICs faces unique challenges, including limited health-care infrastructure, economic constraints and sociocultural barriers[200]. Although preventative strategies have demonstrated efficacy in countries such as China and India, scaling these programmes remains difficult.

A global analysis across 44 LMICs assessed the reach of diabetes mellitus prevention activities, such as physical activity and dietary counselling, among individuals at high risk (defined by IFG, overweight or obesity). Striking disparities emerged in low-income

countries; nearly two-thirds of individuals at high risk reported no engagement in preventive activities, whereas in upper-middle-income countries, ~50% engaged in three or more activities. Younger adults, men and those with less than secondary school education were less likely to receive preventive care. Nonetheless, reports suggest that non-pharmacological preventative strategies may be more feasible in LMICs than in high-income countries owing to their low cost and reduced infrastructure requirements[201]. These findings emphasize the urgency of addressing implementation gaps and tailoring strategies to local contexts and vulnerable populations[202].

Adherence and individual preferences

For effective prediabetes care, aligning interventions with individual goals, values and environmental contexts is crucial. Tailoring approaches to patient preferences improves adherence[203]. A systematic review of 18 studies involving 17,240 individuals with prediabetes[204] revealed variable acceptance of metformin. For instance, increased acceptance was noted among individuals with a family history of diabetes mellitus, Spanish-speaking individuals in English-speaking countries, those seeking weight loss, adolescents with familial diabetes mellitus and individuals with low educational attainment. Women, younger adults and individuals with high BMI exhibited extra attention to prediabetes intervention. Furthermore, racial differences were observed — white individuals often preferred metformin, whereas Black individuals favoured medical nutrition therapy. Non-pharmacological strategies were generally preferred owing to concerns about adverse effects, medication dependence and distrust of the health-care system. Ten studies reported favourable attitudes towards lifestyle interventions, with participants citing physical and mental health benefits[204]. Intensive lifestyle programmes were especially appealing for their broader health impact and minimal adverse effects.

Retention remains a challenge; an analysis of 41,203 individuals in the National DPP in-person lifestyle change programmes reported weekly attrition rates of <1–2%, with 50% of participants remaining in the programme for >28 weeks[205]. Reduced retention was linked to younger age, minority race or ethnicity, limited weight loss, and lower physical activity but was not related to sex. These findings point to the need for targeted maintenance strategies, particularly for younger and minority populations.

Outlook

Prediabetes is a heterogeneous condition that increases the risk of T2DM as well as CVD and other metabolic complications. Discussions regarding the diagnostic criteria and optimal diagnostic tool or strategy to identify individuals with prediabetes are ongoing. Further research is needed to identify simpler modalities, such as non-fasting biomarkers, for the detection of prediabetes. Current evidence also suggests that the two common phenotypes of prediabetes, namely, IFG and IGT, have different pathophysiological bases and may respond differentially to interventions. In particular, efforts focused on identifying why lifestyle modification seems to be relatively ineffective in IFG and what the optimal intervention strategy in such individuals would be are warranted.

Although lifestyle modification remains the intervention of choice for most individuals with prediabetes (especially IGT), the advent of the latest weight loss therapies (pharmacotherapy and metabolic surgery) now offers additional options for favourably altering the natural history of this condition. However, these therapies cannot be recommended on a universal basis given the magnitude of the problem of prediabetes, with implications on cost, safety and patient acceptability. Additionally, many non-Europeans have non-obese prediabetes and T2DM, which may reflect other pathophysiological mechanisms, such as predominant β-cell dysfunction, that may respond less well to weight-reducing strategies[206,207]. More research is required in these populations who account for the majority of the global population with diabetes and prediabetes.

Individuals most likely to benefit from any form of intervention are those with a high risk of progression to T2DM and those with additional indications, for example, obesity, CVD or CKD. Given the heterogeneity in terms of pathophysiology, natural history and responses to treatment, more research is needed to increase the precision of prediction and prevention by stratifying individuals based on genetic risk or metabolic risk so that interventions can be directed to those likely to benefit the most. Sustainability and individual preferences also need to be considered, especially in resource-limited settings where data on the benefits of interventions are scarce. Notwithstanding these challenges, taking on the global problem of prediabetes opens a window of opportunity not only to prevent diabetes mellitus but also diabetes-related comorbidities such as CVD.

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Author contributions

Introduction (R.U. and V.M.); Epidemiology (S.H.W.); Mechanisms/pathophysiology (M.R.); Diagnosis and screening (R.U., V.M. and J.E.S.); Management (A.L.P.); Quality of life (S.O.); Outlook (R.U. and V.M.); overview of the Primer (R.U. and V.M.).

Competing interests

V.M. has acted as consultant and speaker, and received research or educational grants from Abbott, Medtronics, Novo Nordisk, Sanofi, Servier, Boehringer-Ingelheim, Eli Lilly, Johnson & Johnson, Lifescan, Roche, MSD, Novartis, Aventis, Bayer, USV, Dr. Reddy's, Sun Pharma, INTAS, Lupin, Glenmark, Zydus, IPCA, Torrent, Cipla, Biocon, Primus, Franco Indian, Wockhardt, Emcure, Mankind, Fourrts, Apex, GSK and Alembic. M.R. has received lecture fees or served on advisory boards for AstraZeneca, Boehringer-Ingelheim, Echosens, Eli Lilly, Madrigal, MSD, Novo Nordisk and Target RWE and has performed investigator-initiated research with support from Boehringer-Ingelheim and Novo Nordisk to the German Diabetes Center (DDZ). J.E.S. has received lecture fees or served on advisory boards for and/or received honoraria from Zuellig Pharma, AstraZeneca, Sanofi, Novo Nordisk, Eli Lilly, Abbott, Mylan, Boehringer-Ingelheim, Roche, Pfizer and GSK. R.U., S.H.W. and S.O. declare no competing interests.

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